ORAL MATRIX FORMULATIONS OF DOXAZOSIN

Technical Field of the Invention

The present invention relates to extended release pharmaceutical compositions of doxazosin. The compositions include doxazosin, a low viscosity release retarding agent and a high viscosity release retarding agent.

Background of the Invention

Doxazosin, 1-(4-amino-6, 7-dimethoxy -2-quinazolinyl)-4-[(2,3-dihydro-1, 4-benzodioxin-2-yl)-carbonyl]-piperazine monomethanesulfonate and pharmaceutically acceptable acid addition salts thereof are described in U.S. Patent No. 4,188,390. Doxazosin is a quinazoline derivative that acts through selective inhibition of alpha-1 adrenoceptors and is indicated for the treatment of hypertension, either alone or in combination with other antihypertensive agents, urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH).

Doxazosin is well absorbed after oral administration with a bioavailability of 65% and a mean plasma half-life of about 11hrs.

When treating hypertension or symptoms of benign prostatic hyperplasia, doxazosin therapy is initiated at 1 mg standard immediate release dosage form per day. The dose is doubled every 7 to 14 days to a maximum recommended dose of 16 mg per day for hypertension and 8 mg per day for benign prostatic hyperplasia. This regimen can require up to three to four titration steps to achieve therapeutically effective doses in a manner that is likely to avoid first dose side effects. This can be achieved by developing a formulation that has a sustained release of doxazosin which subsequently prolongs the Tmax and reduces the peak to trough blood level fluctuation levels of doxazosin when compared to the standard immediate release dosage form available.

This problem was solved by the development of Cardura-XL osmotic dosage form by Pfizer. The Cardura-XL formulation utilizes an osmotic system to deliver doxazosin for extended period of at least about 24 hours. The advantages of this system are that the release of the drug is pH independent and gastrointestinal motility does not significantly affect the rate of release of the active ingredient. The active ingredient is released from

said osmotic dosage form in a zero order thus controlling the active ingredient delivery rate. However, development of such a system requires sophisticated facilities for techniques, such as laser drilling, and requires skilled people to manufacture the dosage form. Such requirements have implications on overall costs and time of production when compared to a conventional matrix dosage form.

The matrix formulations of the present invention are easy to manufacture, do not require skilled persons and manufacturing operations and are relatively simple and cost effective. The matrix formulations of the present invention releases the drug over extended period of time from about 12 hours to about 24 hours wherein there is a sustained release of doxazosin with a prolonged T_{max} that has reduced peak to trough doxazosin blood level fluctuation. This enhances the pharmacokinetic profile and affords a simplified dosing schedule. The formulations of the present invention may be administered at higher initial daily dose (4 mg per day) than the standard doxazosin 1 mg immediate release tablet, while avoiding significant first pass side effects. The therapeutic effective levels of doxazosin can be reached more rapidly without excessive plasma levels and a more uniform plasma concentration is provided that has minimal peak to trough blood level fluctuation.

European Patent No. 700285 discloses pharmaceutical compositions of alpha adrenoreceptor blocking agents which have a biphasic drug release profile. The pharmaceutical compositions have matrix compositions which include hydroxypropyl methylcellulose and an additional coating which is dissolved by conditions present in the colon.

U.S. Patent No. 4,259,314 discloses a dry pharmaceutical formulation containing a therapeutic agent and a dry carrier comprising hydroxypropyl methylcellulose and hydroxypropyl cellulose. Also disclosed is the use of hygroscopic active ingredients with the formulations.

European Patent No. 862437 discloses a controlled-release pharmaceutical formulation for oral administration consisting essentially of: an active drug compound; low molecular weight polyethylene oxide; hydroxypropylmethyl cellulose; tabletting excipients; and optionally one or more enteric polymers

European Patent No. 0413061 discloses the sustained formulations containing active ingredient and combination of hydroxypropyl methylcellulose and hydroxypropyl cellulose. The hydroxypropyl methylcellulose used therein is selected from two different number average molecular weight of from 30,000 to 350,000; and 9,000 to 30,000.

U.S. Patent No. 6,083,532 discloses sustained release formulations which include at least three different types of polymers including a pH dependent gelling polymer, a pH independent gelling polymer and an enteric polymer. The pH dependent gelling polymer includes at least one of an alginate, a carboxyvinyl polymer, or a salt of a carboxymethyl cellulose.

Summary of the Invention

In one general aspect there is provided an oral matrix pharmaceutical composition of doxazosin or a pharmaceutically acceptable salt thereof. The composition also includes a low viscosity release retarding agent and a high viscosity release retarding agent.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the release retarding agents may include one or more of cellulose derivatives, acrylic acid or methacrylate polymers/copolymers, gums, vinyl alcohol or vinylpyrrolidone based polymers, block copolymers, or polyethylene oxide.

The cellulose derivatives may include one or more of hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose, hydroxyethylcellulose, carboxymethylcellulose, or methylcellulose.

The low viscosity release retarding agent comprises between about 5% to about 40% w/w of the composition or it may be between about 8% to about 25% w/w of the composition.

The high viscosity release retarding agent comprises between about 5% to about 40% w/w of the composition or it may be between about 8% to about 20% w/w of the composition.

The pharmaceutical composition may further include one or more solubility enhancers.

The solubility enhancers may be one or more of polyethylene glycols, surfactants, propylene glycol, glycerol, mono-alcohols, higher alcohols, DMSO, dimethylformamide,

N, N-dimethylacetamide, 2-pyrrolidone; N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted-alkyl-azacycloalkyl- -2-ones.

The pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include one or more of binders, diluents and lubricant/glidants.

The pharmaceutical composition may be in the form of tablets, capsules, pellets, granules or any other dosage forms suitable for oral administration.

The pharmaceutical composition releases the doxazosin over a period of about 12 hours to about 24 hours.

In another general aspect, there is provided an oral matrix pharmaceutical composition of doxazosin or its salt, solvate hydrate, enantiomers or mixture thereof. The pharmaceutical composition also includes about 5% to about 40% w/w of hydroxypropylmethyl cellulose of high viscosity, about 5%to about 40% w/w of hydroxypropyl methylcellulose of low viscosity, about 2% to about 20% w/w of polyethylene glycol, about 15% to about 50% w/w of lactose, about 10% to about 50% w/w of microcrystalline cellulose, about 0.1% to about 3% w/w of magnesium stearate, about 0.1% to about 2% w/w of talc and about 0.1% to about 3% w/w of colloidal silicon dioxide.

In another general aspect, there is provided an oral matrix pharmaceutical composition of doxazosin or a salt, solvate, hydrate, enantiomer or mixture thereof. The pharmaceutical composition also includes about 8% to about 20% w/w of hydroxypropylmethyl cellulose of high viscosity, about 8% to about 25% w/w of hydroxypropyl methylcellulose of low viscosity, about 5% to about 10% w/w of polyethylene glycol, about 20% to about 40% w/w of lactose, about 20% to about 40% w/w of microcrystalline cellulose, about 0.1% to about 3% w/w of magnesium stearate, about 0.1% to about 2% w/w of talc and about 0.1% to about 3% w/w of colloidal silicon dioxide.

In yet another general aspect, there is provided an oral matrix pharmaceutical composition of doxazosin or a salt, solvate, hydrate, enantiomer or mixture thereof. The pharmaceutical composition also includes about 5% to about 40% w/w of hydroxypropyl

methylcellulose of high viscosity, about 5% to about 40% w/w of hydroxypropyl methylcellulose of low viscosity, about 1% to about 20% w/w of sodium alginate and alginic acid, about 5% to about 20% of Eudragit EPO, about 0.1% to about 3% w/w of magnesium stearate, about 0.1% to about 2% w/w of talc and about 0.1% to about 3% w/w of colloidal silicon dioxide.

In another general aspect, there is provided an oral matrix pharmaceutical composition of doxazosin or a salt, solvate, hydrate, enantiomer or mixture thereof. The pharmaceutical composition also includes about 8% to about 20% w/w of hydroxypropyl methylcellulose of high viscosity, about 10% to about 25% w/w of hydroxypropyl methylcellulose of low viscosity, about 2% to about 10% w/w of sodium alginate and alginic acid, about 6% to about 10% w/w of Eudragit EPO, about 0.1% to about 3% w/w of magnesium stearate, about 0.1% to about 2% w/w of talc and about 0.1% to about 3% w/w of colloidal silicon dioxide.

In yet another general aspect, there is provided a method of treating one or more of hypertension, urinary outflow obstruction and symptoms associated with benign protastic hyperplasia in a patient in need thereof. The method includes administering an oral matrix pharmaceutical composition comprising doxazosin or a pharmaceutically acceptable salt thereof, a low viscosity release retarding agent and a high viscosity release retarding agent.

Detailed Description of the Invention

The inventors have now developed a pharmaceutical composition containing doxazosin or a pharmaceutically acceptable salt thereof. The pharmaceutical composition also includes a low viscosity release retarding agent and a high viscosity release retarding agent.

When ingested orally, the pharmaceutical composition of the present invention releases doxazosin over an extended period of time from about 12 hours to about 24 hours. The sustained release of doxazosin causes a prolonged T_{max} and reduces the peak to trough doxazosin blood level fluctuation. This thereby enhances the pharmacokinetic profile and affords a simplified dosing schedule.

Suitable active ingredients include doxazosin or a salt, solvate, hydrate, enantiomer or mixture thereof.

A release retarding agents include any suitable polymer capable of retarding the release of the active ingredient for about 24 hours.

A solubility enhancer suitable agent that is capable of improving the solubility of the active ingredient.

Suitable release retarding ingredient may be selected from cellulose derivatives, acrylic acid or methacrylate polymers/copolymers, gums, vinyl alcohol or vinylpyrrolidone based polymers, block copolymers, polyethylene oxide or such like. The cellulose polymers are selected hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose, hydroxyethylcellulose, carboxymethylcellulose, and methylcellulose. The concentration of release retarding ingredient may be from about 10% to about 70% w/w, preferably from about 20% to about 35% w/w.

Suitable cellulose polymers include hydroxypropyl methylcellulose 2208 of different viscosity grades. These polymers are categorized as low viscosity polymers having viscosity between about 5 to about 100cps and as high viscosity polymers high viscosity polymers having viscosity greater than about 101 cps.

Suitable low viscosity polymers include Methocel E-5 and Methocel K100LVCR, sold by Dow Chemical Co. The low viscosity polymer may be present at a concentration of between about 5% to about 40% w/w, and preferably from about 8% to about 25%.

Suitable high viscosity polymers include Methocel K-4MCR, Methocel K 15 M CR and Methocel K100MCR. The high viscosity polymer may be present at a concentration of between about 5% to about 40% w/w, preferably from about 8% to about 20% w/w

Suitable gums include one or more of xantham gum, caraya gum, locust bean gum, sodium alginate, and alginic acid. The pharmaceutical composition may include between about 1% to about 20% w/w of sodium alginate and alginic acid, preferably from about 2%to about 10% w/w.

Suitable acrylic acid or methacrylic/methacrylate based polymers include Eudragits, such as Eudragit L-100, L30 D-55, L-100 55, and S-100, EPO. The pharmaceutical composition may include from about 5% to about 20% w/w of Eudragit EPO, preferably from about 6% to about 10% w/w.

Suitable solubility enhancers include one or more of polyethylene glycols, surfactants, propylene glycol and glycerol; mono-alcohols, such as ethanol, propanol, and higher alcohols; DMSO; dimethylformamide; N, N-dimethylacetamide; 2-pyrrolidone; N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted-alkyl-azacycloalkyl- -2-ones. For example, the solubility enhancer may be polyethylene glycol. The solubility enhancer may be present at between about 2% to about 20% w/w, preferably from about 5-% to about 10% w/w.

The pharmaceutical composition may also include one or more pharmaceutically acceptable excipients. Suitable pharmaceutically acceptable excipients include one or more of binders, diluents and lubricant/glidants.

Suitable binders include one or more of polyvinyl pyrrolidone, pregelatinized starch and gelatin, gums, microcrystalline cellulose. For example, the binder may be Avicel PH 102. The binder may be present at a concentration of between about 10% to about 50% w/w, preferably from about 20% to about 40%.

Suitable diluents include one or more of lactose, mannitol and microcrystalline cellulose. For example, the diluent may be lactose. The diluent may be present at a concentration of between about 15% to about 50% w/w, preferable from about 20% to about 40% w/w.

Suitable lubricants/glidants include one or more of magnesium stearate, zinc stearate, talc and colloidal silicon dioxide. The one or more lubricants/glidants may be present at a concentration between about 0.1% and about 3% w/w. For example, the lubricant/glidant may be magnesium stearate.

In one embodiment, the oral matrix formulation includes doxazosin or its salt, solvate hydrate, enantiomers or mixture thereof, about 5% to about 40% w/w of hydroxypropylmethyl cellulose of high viscosity, about 5%to about 40% w/w of hydroxypropyl methylcellulose of low viscosity, about 2% to about 20% w/w of polyethylene glycol, about 15% to about 50% w/w of lactose, about 10% to about 50% w/w of microcrystalline cellulose, about 0.1% to about 3% w/w of magnesium stearate, about 0.1% to about 2% w/w of talc and about 0.1% to about 3% w/w of colloidal silicon dioxide.

In yet another embodiment, the oral matrix formulation includes doxazosin or a salt, solvate, hydrate, enantiomer or mixtures thereof, about 8% to about 20% w/w of hydroxypropylmethyl cellulose of high viscosity, about 8% to about 25% w/w of hydroxypropyl methylcellulose of low viscosity, about 5% to about 10% w/w of polyethylene glycol, about 20% to about 40% w/w of lactose, about 20% to about 40% w/w of microcrystalline cellulose, about 0.1% to about 3% w/w of magnesium stearate, about 0.1% to about 2% w/w of talc and about 0.1% to about 3% w/w of colloidal silicon dioxide.

In another embodiment, the oral matrix composition includes doxazosin or a salt, solvate, hydrate, enantiomer or mixtures thereof, about 5% to about 40% w/w of hydroxypropyl methylcellulose of high viscosity, about 5% to about 40% w/w of hydroxypropyl methylcellulose of low viscosity, about 1% to about 20% w/w of sodium alginate and alginic acid, about 5% to about 20% of Eudragit EPO, about 0.1% to about 3% w/w of magnesium stearate, about 0.1% to about 2% w/w of talc and about 0.1% to about 3% w/w of colloidal silicon dioxide.

In another embodiment, the oral matrix composition includes doxazosin or a salt, solvate, hydrate, enantiomer or mixtures thereof, about 8% to about 20% w/w of hydroxypropyl methylcellulose of high viscosity, about 10% to about 25% w/w of hydroxypropyl methylcellulose of low viscosity, about 2% to about 10% w/w of sodium alginate and alginic acid, about 6% to about 10% w/w of Eudragit EPO, about 0.1% to about 3% w/w of magnesium stearate, about 0.1% to about 2% w/w of talc and about 0.1% to about 3% w/w of colloidal silicon dioxide.

The sustained release composition may be in the form of tablets, capsules, pellets, granules or other dosage forms suitable for oral administration. The tablets may be prepared by techniques like direct compression, wet granulation or dry granulation. The tablets may be optionally coated with a non functional coating. The tablet/minitablets may be optionally filled into capsules

The following non-limiting examples illustrate the process for making the sustained release composition disclosed in various embodiments of the specification.

Example 1

S.No	Ingredients	%
1	Doxazosin Mesylate	3.42
2	Polyethylene glycol	8.77
3	Lactose	45.61
4	Microcrystalline cellulose	22.87
5	Methocel K100MCR	8.77
6	Methocel K100LVCR	8.77
7	Mg. Stearate	0.701
8	Talc	0.701
9	Colloidal silicon dioxide	0.35

Process:

Step 1: PEG melted on water bath and Doxazosin added to it and cooled with mixing. The cooled material is passed thru BSS # 44. All other excipients were sifted through British Standard Sieve 44#.

Step 2: Methocel K100MCR, Methocel K100LVCR & Lactose were mixed in double cone blender for 20 minutes to obtain a blend

Step 3: The granules of Polyethylene glycol & Doxazosin Mesylate & Microcrystalline cellulose were mixed in double cone blender for 20 minutes to obtain a blend. Both the blends of step 2 and 3 were mixed in a double cone blender for 20 minutes to obtain a blend.

Step 4: Talc and Colloidal silicon dioxide were mixed with blend of step 3 for 5 minutes followed by mixing Magnesium stearate for 5 minutes and was compressed to form tablets using 9mm Punch.

Example 2

S.No	Ingredients	%
1	Doxazosin Mesylate	3.56
2	Polyethylene glycol	5.45
3	Lactose	36.43
4	Methocel E-5	21.81
5	Methocel K-4MCR	14.54
6	Sodium alginate	3.636
7	Alginic Acid	5.45
8	Eudragit EPO	7.27
9	Mg. Stearate	0.727
10	Talc	0.727
11	Colloidal silicon dioxide	0.363

Process:

Step 1: PEG melted on water bath and doxazosin added to it and cooled with mixing. The cooled material is passed thru BSS # 44. All other excipients were sifted through British Standard Sieve 44#. All the excipients were sifted through British Standard Sieve 44#.

Step 2: Methocel E-5, Methocel K-4MCR, Sodium alginate, Alginic acid, Eudragit EPO were mixed in double cone blender for 20 minutes to obtain a blend.

Step 3: The granules of polyethylene glycol and doxazosin mesylate & lactose were mixed in double cone blender for 20 minutes to obtain a blend. Both the blends of step 2 and 3 were mixed in a double cone blender for 20 minutes to obtain a blend.

Step 4: Talc and colloidal silicon dioxide were mixed with blend of step 3 for 5 minutes followed by mixing magnesium stearate for 5 minutes and was compressed to form tablets using 9mm punch.

Example 3

S.No	Ingredients	%
1	Doxazosin Mesylate	3.01
2	Polyethylene glycol	7.69
3	Microcrystalline cellulose	35.38
4	Lactose	24.67
5	Methocel K100M CR	12.307
6	Methocel K100LV CR	15.38
7	Magnesium Stearate	0.615
8	Talc	0.615
9	Colloidal silicon dioxide	0.307

Process:

Step 1: PEG melted on water bath and doxazosin added to it and cooled with mixing. The cooled material is passed thru BSS # 44. All other excipients were sifted through British Standard Sieve 44#. All the excipients were sifted through British Standard Sieve 44#.

Step 2: Methocel K100MCR, Methocel K100LVCR and lactose were mixed in double cone blender for 20 minutes to obtain a blend

Step 3: The granules of polyethylene glycol, doxazosin mesylate and microcrystalline cellulose were mixed in double cone blender for 20 minutes to obtain a blend. Both the blends of step 2 and 3 were mixed in a double cone blender for 20 minutes to obtain a blend.

Step 4: Talc and colloidal silicon dioxide were mixed with blend of step 3 for 5 minutes followed by mixing magnesium stearate for 5 minutes and was compressed to form tablets using 9mm punch.

Example 4

S.No	Ingredients	%
	Intragnular	
1	Doxazosin Mesylate	3.21
2	Lactose	32.521
3	Methocel E-5	3.27
4	Citric acid *	16.39
	Extragranular	
5	Methocel E-5	16.39
6	Sodium alginate	3.27
7	Methocel K-4 MCR	11.47
8	Alginic acid	4.91
9	Eudragit EPO	6.55
10	Magnesium Stearate	0.983
11	Talc	0.65
12	Colloidal silicon dioxide	0.327

* PEG 6000 / Tartaric Acid / Lutrol F 407 / any other solubilizer / no solubilizer

Process:

Step 1: doxazosin mesylate was sifted through British Standard Sieve 22# and all other excipients were sifted through British Standard Sieve 44#

Step 2: Lactose, Methocel E-5 and citric acid (tartaric acid, malic acid, fumaric acid, maleic acid and / or any other solublizer) were mixed for 20 minutes to obtain a blend and the blend of step 2 was mixed with doxazosin mesylate for 15 minutes to obtain a blend.

Step 3: Magnesium stearate was added to the blend of step 3 with above blend and mixed for 5 minutes to obtain a blend.

Step 4: Slugs were prepared of blend of step 3 and were broken and passed through British Standard Sieve 22# to obtain granules.

Step 5: Methocel E-5, Methocel K-4MCR, Keltone LVCR, alginic Acid, Eudragit EPO were mixed to obtain a blend.

Step 6: Granules of Step 4 and blend of Step 5 were mixed for 20 minutes to obtain a blend.

Step 7: Talc and colloidal silicon dioxide were mixed with blend of step 3 for 5 minutes followed by mixing magnesium stearate for 5 minutes and was compressed to form tablets using 9mm Punch.

Example 5: Doxazosin 4 mg strength

S.N.	Ingredients	%
1	Doxazosin Mesylate	1.49
2	Polyethylene glycol	3.85
3	Microcrystalline cellulose	35.38
4	Lactose	24.7
5	Methocel K100M CR	14.68
6	Methocel K100LV CR	18.35
7	Magnesium Stearate	0.615
8	Talc	0.615
9	Colloidal silicon dioxide	0.307

The process of example 1 is followed to prepare the above formulation.

The optional coating with Opadry white or with following representative example may be used to coat doxazosin dosage form.

Ingredient	Percentage
Eudragit L 100 55:	22.4
NaOH:	0.3
PEG:	2.9
HPMC E 5:	67.2
Talc	6.7
Titanium dioxide:	0.5
Water	q.s.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.